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EXAMINER	
KOLKER, DANIEL E	
ART UNIT	**PAPER NUMBER**
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/724,288	SCHENK ET AL.	
	Examiner	Art Unit	
	DANIEL KOLKER	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *92,97,98 and 100-102* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *98 and 100* is/are allowed.

6)☒ Claim(s) *92,97,101 and 102* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/28/08, 8/29/08 (5 IDSs), 10/3/08 (2 IDSs)*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks and amendments filed 18 September 2008 have been entered. Claims 92, 97 – 98, and 100 – 102 are pending and under examination.

Withdrawn Rejections

2. The following rejections set forth in the previous office action are withdrawn:

A. The rejection of claim 100 under 35 USC 103(a) is withdrawn in light of the arguments. Ard teaches that the failure of microglia to phagocytose Ab from tissue samples from Alzheimer's patients is most likely due to the presence of complexes within the tissue that prevent the microglia from effectively processing microglia (p. 201 second column end of first complete paragraph).

B. The rejection of claim 98 under 35 USC 103(a) is withdrawn in light of the arguments. Applicant persuasively argues that antibodies raised against residues 1 – 7 of Aβ are more effective in stimulating phagocytosis than those raised against some other regions tested, and points to Table 16 on p. 97 of the specification as providing evidence. Consistent with the guidance in MPEP § 2145, rejections under 35 USC 103(a) should be withdrawn when evidence of unexpected results is presented. The examiner concedes that there was nothing in the prior art of record specifically suggesting that antibodies that bind residues 1 – 7 of Aβ are more effective in stimulating phagocytosis.

Maintained Rejections

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 92 and 97 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ard (1996. Journal of Neuroscience Research 43:190-202,) in view of Ulvestad (1994. Journal of Neuropathology and Experimental Neurology 53:27-36).

This rejection stands for the reasons previously made of record and explained in more detail below. Briefly, Ard teaches methods of contacting amyloid deposits with several compounds, including serum (which comprises antibodies), leupeptin, and cell culture medium, and adding the composition (i.e., both the amyloid deposit and the test agents) to microglial cells. This is a screening method and is on point to claims 92 and 97. Ard teaches that cultured microglia have the ability to clear Aβ peptide (see abstract, see also Figure 1) and teaches contacting Aβ with microglia, followed by a series of measurements to determine whether a reduction in the amount of amyloid deposit occurs; see p. 196 and Figures 6 – 9). Ard teaches that microglia are capable of removing Aβ peptide from solutions (see p. 199 top of second column). However Ard does not explicitly teach combining the amyloid deposit with the antibody prior to adding microglial cells and does not teach adding an antibody that binds to Aβ as recited in claim 92 and does not explicitly teach screening monoclonal antibodies as recited in claim 97.

Ulvestad teaches that microglia have Fc receptors on their surface, which is on point to claims 92 and 97. Ulvestead also teaches that when contacted with immune complexes comprising antibodies bound to their cognate antigen, Fc receptors on microglia become active and the microglia phagocytose their targets (see abstract, see also p. 34 first column final paragraph and p. 34 second column first complete paragraph). Ulvestad teaches contacting antibodies and their antigen (here, erythrocytes and antibodies, referred to as EA) with one another prior to contacting them with microglia (p. 29, phagocytosis assay). However Ulvestad does not teach contacting samples comprising amyloid deposits with microglia and does not explicitly teach using monoclonal antibodies for activating Fc receptors, although the reference does report that monoclonals can be used for other purposes.

It would have been obvious to one of ordinary skill in the art to modify the methods of Ard by contacting the samples comprising amyloid deposits with antibodies prior to adding microglia, as suggested by Ulvestad, with a reasonable expectation of success. The motivation

to do so would be to activate the Fc receptors on the microglia, which Ulvestad teaches is a necessary step in activating the phagocytic activity of these cells and would be required to successfully identify antibodies that bind to Aβ amyloid deposits and are subsequently phagocytosed by microglia. While neither of the references explicitly teaches using an antibody against Aβ, doing so would have been obvious to one of ordinary skill in the art given the teachings of Ulvestad. Ulvestad teaches that immune complexes comprised of an antibody bound to its antigen are what activate Fc receptors. Since Ard teaches that microglia can clear Aβ, and Ulvestad teaches that antigen-antibody complexes are cleared more rapidly than the antigen alone, selecting an anti-Aβ antibody and incubating it with the amyloid deposit would have been obvious, as this would allow for formation of the immune complex, which Ulvestad teaches is cleared by microglia.

Additionally, it would have been obvious to one of ordinary skill in the art to modify the method of Ard by including monoclonal antibodies, thereby arriving at the inventions of claim 97. Doing so would have been obvious, as monoclonals have an intact Fc region.

Applicant argues that the claimed method would not have been obvious to one of ordinary skill in the art. Specifically, applicant argues that since Ard did not see phagocytosis when serum was added, and the examiner has contended that serum comprises antibodies, there would have been no motivation to add antibodies, as that would not lead to the claimed invention. Applicant also argues that Ard's goal was not screening of antibodies but identifying systems that fail in Alzheimer's disease. Finally, applicant argues that there is no teaching that the binding of an antibody to Aβ is required for phagocytosis, so inclusion of one would not have been obvious. Applicant's arguments have been fully considered but they are not persuasive.

With respect to the first argument, the examiner acknowledges that addition of serum decreased phagocytosis. The examiner had indicated that serum comprises antibodies solely to provide evidence that the contacting step recited in claim 92 is provided for. Of course given the most recent amendment of claim 92, even this point is now moot, as the claim requires contacting the amyloid deposit with an antibody specific for Aβ, which is not explicitly taught by Ard. Nonetheless, Ard attributes the decreased phagocytosis to the effects of other proteins present in serum, not to antibodies; see p. 201 first column first complete paragraph. The motivation to add antibodies against Aβ comes from Ulvestad, who teaches that antibodies bound to their cognate antigen activate Fc receptors and are rapidly cleared by microglia.

With respect to the argument that since Ard's goal was not to screen antibodies, there would have been no motivation to screen antibodies, the arguments are not persuasive. Ard was clearly investigating both the phenomenon of clearance of Aβ by microglia as well as what physiological systems might break down in Alzheimer's disease. Ard certainly mentions that one hypothesis is that factors within the body inhibit clearance and phagocytosis and indicates that discovery of such factors may advance understanding of the disease process. But one of ordinary skill in the art would be motivated to also find agents which accelerate the clearance process. Since Ard clearly shows that microglia can phagocytose Aβ, the artisan of ordinary skill, reading both Ard and Ulvestad, would have been motivated to form complexes between Aβ and anti- Aβ antibodies in order to determine whether these are more efficiently cleared. There would have been a reasonable expectation of success, as Ulvestad teaches that an antibody bound to its antigen is phagocytosed more efficiently than the antigen alone.

With respect to the argument that there is no teaching that binding an antibody to Aβ is required for phagocytosis, so inclusion of one would not have been obvious, the argument is not persuasive. The reference by Ulvestad clearly teaches that microglia clear immune complexes (see p. 34 second column first complete paragraph), and given that Ard teaches that Aβ is cleared by microglia, the artisan of ordinary skill would have found it obvious to include antobodies that bind to Aβ, as this would likely increase the rate of phagocytosis.

On pp. 7 – 8 of the remarks filed 18 September 2008, applicant argues that there would not have been a reason or motivation to include a monoclonal antibody, as required by claim 97. Applicant argues that the monoclonals from Ulvestad were not used to activate Fc receptors, so it would not have been obvious to use them. This argument has been fully considered but is not persuasive. The examiner acknowledges that monoclonals were not used by Ulvestad for the purpose of activating Fc receptors. However, Ulvestad does teach monoclonal antibodies, and they were well-known in the art at the time the invention was made, and offer several advantages over polyclonal antibodies including that the hybridoma that produces them can make an essentially limitless supply. Thus using monoclonal antibodies would have been obvious to one of ordinary skill in the art.

Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 103

4. Claims 92, 97, and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ard in view of Ulvestad as applied to claims 92 and 97 above, and further in view of Becker (EP 0 613 007, published 31 August 1994, cited as reference 44 on IDS filed 10 September 2001).

The reasons why claims 92 and 97 are obvious over Ard in view of Ulvestad are set forth in the rejection under 35 USC 103(a) above. However neither reference explicitly teaches selection of chimeric, humanized, or human antibodies as recited in claim 101.

Becker teaches that antibodies that bind to Aβ are useful as therapeutics for Alzheimer's disease; see column 7 lines 39 – 52 for example. Becker indicates that any of several forms of antibodies can be used, including monoclonals as recited in claim 97, as well as chimeric and humanized antibodies as recited in new claim 100; see column 5 line 51 – column 6 line 53. However Becker does not teach the screening assays of claims 92 and 97.

It would have been obvious to one of ordinary skill in the art to use the monoclonal, chimeric, or humanized antibodies that bind Aβ taught by Becker in the assays rendered obvious by Ard in view of Ulvestad. The motivation comes directly from the references themselves, as Ulvestad indicates that antibodies bound to their antigen are effectively cleared by microglia, and Becker teaches that these particular types of antibodies against Aβ are particularly suited to therapy for Alzheimer's disease.

5. Claims 92, 97, and 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ard in view of Ulvestad as applied to claims 92 and 97 above, and further in view of Games 1995 (Nature 373(6514):523-527, cited as reference 109 on IDS filed 10 September 2001).

The reasons why claims 92 and 97 are obvious over Ard in view of Ulvestad are set forth in the rejection under 35 USC 103(a) above. However neither reference explicitly teaches administration of the antibody to a transgenic animal model predisposed to amyloidogenic disease as recited in claim 102.

Games teaches PD-APP mice, which overexpress a mutant form of Aβ and are predisposed to Alzheimer's-type pathology. At p. 527 final paragraph Games teaches that the mice can be used to verify if those agents which appear to be therapeutic for Alzheimer's disease in vitro ameliorate pathology in vivo. However Games does not teach the screening assays of claims 92 and 97.

It would have been obvious to one of ordinary skill in the art to administer the antibodies identified as putative therapeutics in the assays rendered obvious by Ard in view of Ulvestad to the transgenic mice from Games, thereby arriving at the invention of claim 102. The motivation to do so comes directly from Games, who indicates that the mice will be useful to determine whether compounds identified in *in vitro* assays are therapeutic *in vivo*.

Conclusion

6. Claims 92, 97, and 101 – 102 are rejected.

7. Claims 98 and 100 are allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANIEL KOLKER whose telephone number is (571)272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
December 18, 2008